Regioselective modification of carbohydrates for their application as building blocks in synthesis

Zhang, Ji

Chapter 1

Selective modification of the anomeric and the secondary hydroxyl groups in carbohydrates

Regioselective functionalization of hydroxy groups in carbohydrates is very useful. Compared with classical modification of carbohydrates that relies on protecting group strategies, regioselective functionalization or late-stage functionalization is more efficient. It readily provides access to sugar containing molecules. In addition it is also helpful in drug discovery. In this chapter, the recent progress in selective modifications of anomeric hydroxyl and secondary hydroxyl groups in carbohydrates is presented. The reagent 2-chloro-1,3-dimethylimidazolinium chloride (DMC) has been used by Shin-ichiro Shoda in the modification of the anomeric hydroxyl group in free sugars. The synthesis of glycoconjugates such as glycosyl azides, glycosyl triazoles, glycosyl thiols can be performed in the presence of DMC from free sugars. The selective alkylation, deoxygenation or oxidation of the other secondary hydroxyls can be achieved with suitable catalysts via diol chelation.

1.1 Introduction

Carbohydrates play a vital role in biological processes, such as cell-cell interactions, cellular transport, immunology and as energy source. They are major components of the cell walls of most fungi, bacteria and plants. The chemical synthesis and modification of carbohydrates, collected under the common denominator "carbohydrate chemistry", most often rely on protecting and activating group strategies. Although these strategies can be very elegant, and allow the manipulation of carbohydrates in common organic solvents, they tend to add a lot of synthetic steps to the route. In addition, in oligosaccharides protecting group strategies are often not viable. In recent years, the regioselective modification of scarcely or fully unprotected carbohydrates has shown a rapid growth. Here I have chosen to show some of the most recent work that modifies unprotected or partly protected carbohydrates as an introduction to my own work.

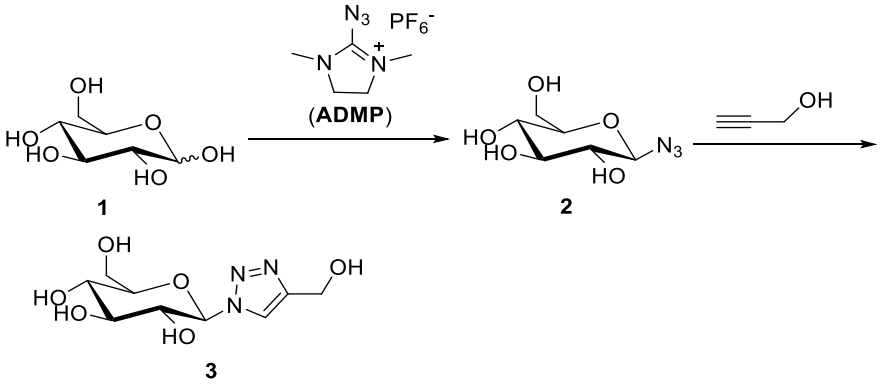
1.2 Modification of the anomeric position

In carbohydrates, the hydroxyl group at the anomeric position stands out from the other hydroxyl groups in (1) that it is part of a hemiacetal, which is in equilibrium with the aldehyde and (2) that its *pK*a (≈ 12.5) is much lower than that of the other hydroxyl groups.[1] Traditionally, the anomeric position is modified by functionalizing of the aldehyde with imine chemistry, Wittig reactions, condensation reactions, oxidation and acetal formation. Recently, the difference in *pK*a has been started to be exploited to protect or activate this position as well.[2]

1.2.1 One-pot synthesis of glycoconjugates directly from reducing sugars

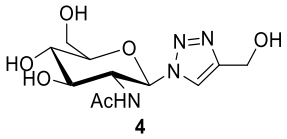
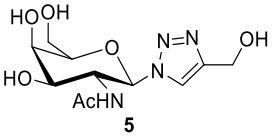
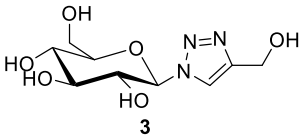
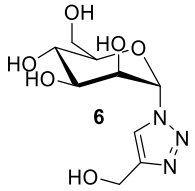
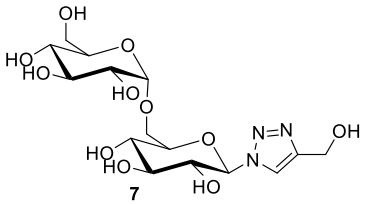
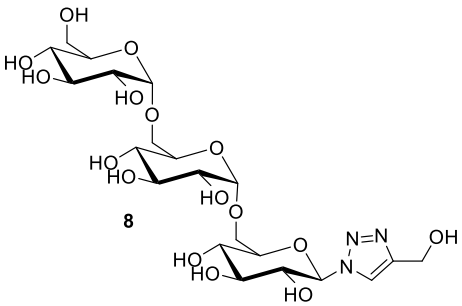
In nature, carbohydrates often exist as glycoconjugates, including glycopeptides, glycolipids etc. Glycoconjugates are of great importance in carbohydrate-protein interations and are also important in chemical biology and medicinal chemistry. The preparation of glyconjugates directly from unprotected reducing sugars is an alternative to classic protecting group methods, it will reduce the number of tedious protection/deprotection steps. The anomeric hydroxyl of a reducing sugar is, due to its lower pKa and because it is hemiacetal,

much more readily modified.[2] Noguchi *et al.* first reported the preparation of carbohydrate oxazolines from reducing sugars with 2-chloro-1,3-dimethylimidazolinium chloride (DMC).[3] Not too long later, they published the synthesis of glycosyl azides with DMC and reducing sugars.[4] This is important because they opened the door to prepare glycosyl azides from unprotected sugars. After that, the use of DMC was extended to the synthesis of pyridyl thioglycosides,[5] sugar peptides,[6] glycosyl thiols[7] and sugar nucleoside diphosphates.[8] Glycosides azides have been used widely in preparing triazoles via Huisgen cycloaddition.[9] If these two processes can be combined in a one-pot reaction, it would be particularly attractive since it allows free sugars to be transformed in glycoconjugates without the process of protection and deprotection.[10] The initially reported method requires the addition of ten or more equivalents of NaN_3 to prepare glycosyl azides with DMC, which hampers a one pot procedure. By replacing DMC with 2-azido-1,3-dimethylimidazolium hexafluorophosphate (ADMP, see structure in scheme 1),[11,12] the anomeric hydroxy group can be activated without the need of an additional source of azide.



Scheme 1. Synthesis of glycosyl azides and glycosyl triazoles via ADMP

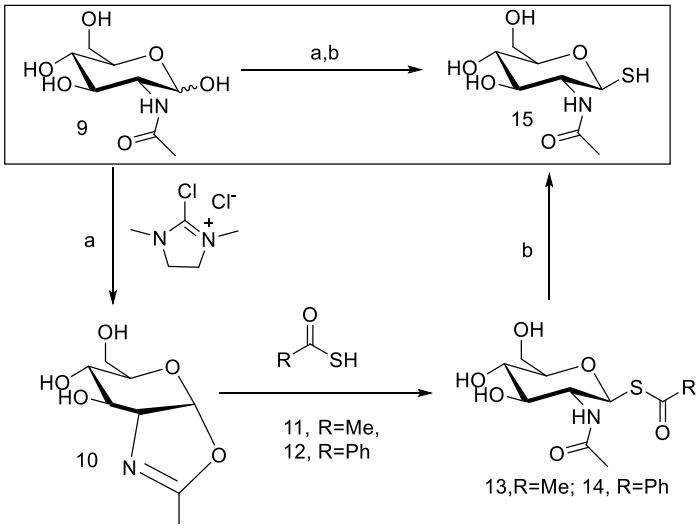
Table 1. One-pot synthesis of glycosyl triazoles directly from the corresponding reducing sugars in water.

#	Sugar	Product	Yield	α/β
1	GlcNAc	 **4**	86%	β only
2	GalNAc	 **5**	75%	β only
3	Glucose	 **3**	73%	β only
4	Mannose	 **6**	73%	α only
5	Isomaltose	 **7**	86%	β only
6	Isomaltotriose	 **8**	88%	β only

Instead the azide that is liberated from the activating agent serves as the nucleophile in the reaction. Dissolving ADMP (3 eq) with a reducing sugar in a mixture of D_2O and MeCN (4:1) containing an excess of Et_3N gave the corresponding β-azide in good yield.[8] After the formation of the glycosyl azide

had completed, propargyl alcohol, copper sulfate and sodium ascorbate were added. Subsequent heating the reaction mixture at 50 °C led to the formation of the desired glycosyl triazole with complete stereoselectivity. Glucose, *N*-acetyl glucosamine, *N*-acetyl galactosamine, mannose, isomaltose and isomaltotriose all gave the β-product, except for mannose which as expected gave the α-glycosyl triazole (Table 1).[10]

1.2.2 One-pot synthesis of uprotected anomeric glycosyl thiols

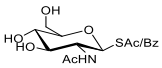
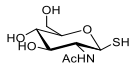
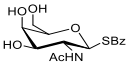
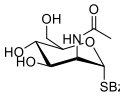
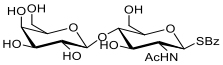
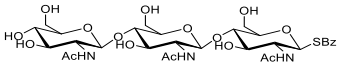
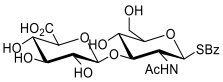
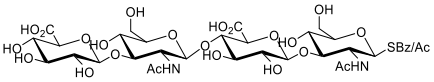
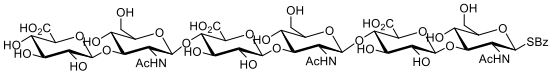


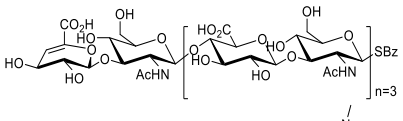
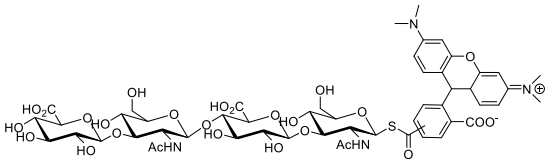
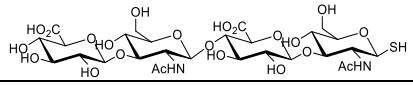
Scheme 2. Protecting-group-free conversion of saccharides into glycosyl thiols. Reaction conditions: a) NEt_3, D_2O/MeCN 2:1, 0 °C→RT, 90 min; thioacid **11** or **12** in MeCN, 5 min; b) NaOMe, MeOH, Dowex H^+-resin. DMC = 2-chloro-1,3-dimethylimidazolinium chloride.

DMC can be used to convert reducing sugars to glycosyl thiols. Classical routes to prepare unprotected anomeric glycosyl thiols always involve the use of fully protected and highly reactive sugar donors. Therefore, these reactions are very sensitive to the presence of water. With the aim of producing 1-glycosyl thiols directly from reducing sugars, Jörg Rademann *et al.*[13] selected GlcNAc as a model compound and reacted it with various sulfur nucleophiles (sodium hydrogen sulfide, sodium sulfide, trityl thiol, *tert*-butylthiol) first in the presence of base and DMC. However, the reactions did not give the expected thiol product. Rather the sulfur nucleophiles reacted with DMC directly. Because GlcNAc formed the intermediate oxazoline **10** first in the presence of DMC (as shown in scheme 2), and **10** was stable under basic conditions, it did not react with sulfur

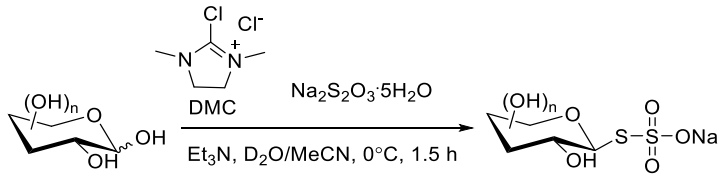
nucleophiles. In order to circumvent nucleophilic substitution of DMC by the sulfur nucleophiles, they activated GlcNAc with DMC and trimethylamine. After that, they tried thiolactic acid **11** and thiobenzoic acid **12** in the reaction. The formed oxazoline **10** is stable, but does react with thiolactic acid **11** or thiobenzoic acid **12** to form 2-acetamido-glucosyl 1-β-thioesters **13** and **14** with completely stereoselectivity. Subsequent treatment of these thioesters with NaOMe furnished β-2-acetamido-2-deoxy-D-glucosamine thiol **15**. This new method was extended to a selection of 2-acetamido-2-deoxy-hexosamines as shown in table 2, all of them gave moderate to excellent yields of the corresponding thioesters.

Table 2. Anomeric glycosyl-1-thiolbenzoates, 1-thiol acetate and 1-thiols.

Substrate	Product	number	Yield[%]
GlcNAc		**13** (Ac) **14** (Bz)	86 90
GlcNAc-SBz		**15**	99
GalNAc		**16**	60
ManNAc		**17** (Bz) **18** (Ac)	80 58
LacNAc		**19**	90
(GlcNAc)$_3$		**20**	65
HA-2		**21**	79
HA-4		**22** (Bz) **23** (Ac)	74 56
HA-6		**24**	63

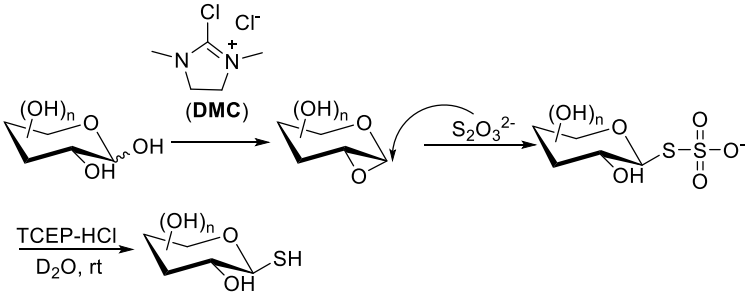
ΔHA-8		**25**	60
HA-4		**26**	35
HA-4-SBz		**27**	97

A limitation of the route by Rademann and coworkers is that it is only suitable for the modification of 2-acetamido-2-deoxy-hexosamines. This limitation was elegantly addressed by Shoda and coworkers.[14]



Scheme 3. one-step synthesis of unprotected glycosyl thiosulfates ("glycosyl Bunte salts")

They reported a one-step synthesis of unprotected glycosyl thiosulfates by using $Na_2S_2O_3$. The DMC-mediated condensation reactions reported by them first used D-glucose, NMR showed the product had β-stereochemistry. They reasoned that this β-selectivity could be due to neighboring participation of 2-OH, which leads to the formation of 1,2-anhydroglucose (see scheme 4). Attack of this epoxide intermediate by sodium thiosulfate will exclusively yield the β-anomer.



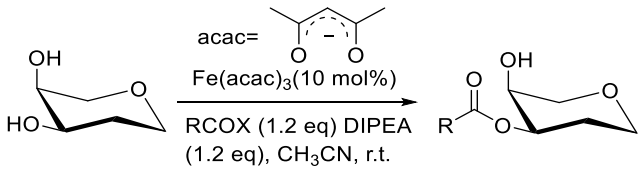
Scheme 4. The mechanism to form the β-anomer

To validate the hypothesis, 3-*O*-methylglucose, 4-*O*-methylglucose, 4,6-*O*-benzylidene glucose were tested and gave excellent β-selectivity. However, 2-*O*-methylglucose gave the corresponding product with lower yield and poor selectivity because there is no 2-OH neighboring participation to form the 1,2-anhydroglucose intermediate.. The reaction was also applied to allose, xylose, mannose, galactose and rhamnose, all provided the corresponding glycosyl thiosulfates. When *N*-acetylglucosamine was used as a substrate, the reaction did not work, because neighboring participation of 2-acetamido leads to the formation of the oxazoline, which is quite stable towards attack by the thiosulfate ion. As a solution to this problem, Shoda used hydrochloric acid to activate the oxazoline ring to afford the glycosyl thiosulfates, this situation is similar to the work of Rademann and coworkers.[13] In the end, shoda cleaved β-glucosyl Bunte salt with the aid of tris(2-carboxyethyl) phosphine hydrochloride (TCEP-HCl) to yield the corresponding 1-thioglucose with high yield.

1.3 Site selective modification of the other secondary alcohols

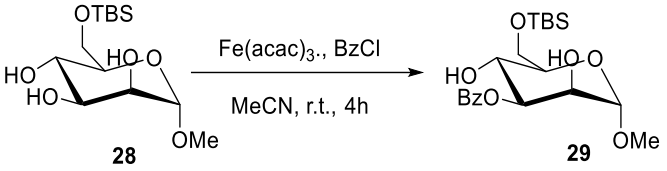
Selective modification of secondary hydroxyl groups is a challenge, because of the similarity in the characteristics of secondary hydroxyls of carbohydrates. How to take advantage of the small differences in reactivity is the key step in this research. At present, chelation with *cis* or *trans* diols in carbohydrates via catalysts is a solution to this regioselectivity. In this chapter, selective functionalization of secondary hydroxy groups in carbohydrates is all based on the chelation of catalysts with hydroxyl groups. Chelation with catalysts is a powerful tool for the selective modification in carbohydrate chemistry, so catalysts for the selective modification in carbohydrates is promising and deserves more efforts to develop.

1.3.1 Site-selective acylation of carbohydrates containing 1,2-*cis*-diols



Scheme 5. Iron (III)-catalyzed regioselective acylation of carbohydrates containing a cis-vicinal diol

Regioselective, or perhaps better "site-selective" protection of carbohydrates is a challenge in synthesis, since this class of compounds possess a lot of very similar hydroxyl groups. Suitable catalysts are now developed that selectively recognize one or some of the OH groups in monosaccharides. As an example, Hai Dong et al.[15] recently described the catalyst $Fe(acac)_3$ for the site-selective acylation of 1,2-*cis*-diols (Scheme 5). As for this and most other examples, it is mostly not clear whether the site selectivity is brought about by catalyst control or substrate control.



Scheme 6. Iron (III)-catalyzed regioselective acylation of **28**

As a test substrate for the regioselective benzoylation with benzoyl chloride (1.2 eq) in the presence of DIPEA (1.5 eq) and a catalytic amount of $Fe(acac)_3$ (0.05-0.2 eq), methyl-6-*O*-(tertbutyldimethylsilyl)-α-D-mannopyranoside was used. This substrate provided the 3-*O*-benzoylated product (Scheme 6) with a high regioselectivity. The observation that the acyl group was added preferentially to the equatorial hydroxyl group prompted the authors to extend this reaction to more manno-type and galacto-type compounds. The authors noted that some substrates gave side products with acylated axial hydroxyl groups but reasoned that this was probably not due to lower selectivity of the initial acylation but a result of migration of the acyl group from the equatorial to the axial position due to the excess of DIPEA in combination with the high temperature. This undesired side reaction could be suppressed by reducing the amount of DIPEA from 1.5 eq to 1.2 eq, in combination with a decrease in reaction temperature.

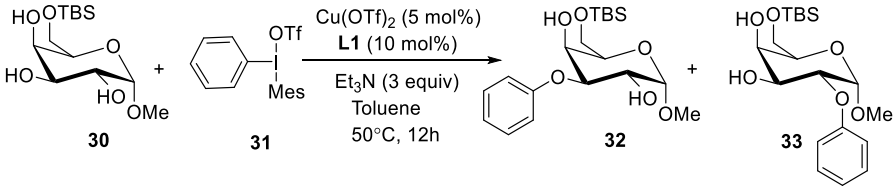
1.3.2 Site-selective *O*-alkylation and arylation of glycosides

An alternative means to functionalize carbohydrates is the selective alkylation and arylation of unprotected and partly protected carbohydrates and this has started to attract significant attention from the synthetic community. Generally, this reaction involves the use of organo-borinic acids, organotin reagents, or other Lewis acid catalysts. As organotin compounds are inherently

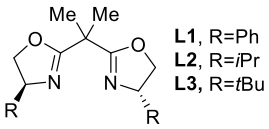
toxic, Niu *et al*[16] pioneered the arylation of monosaccharides with diaryliodonium reagents (that are consider to be non-toxic) catalyzed by copper catalysts. On galactose these conditions furnish the C3-OH arylated product, as depicted in table 3.

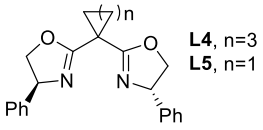
Niu et al[16] screened a series of ligands as shown in table 3 and the results showed that the ligand is essential for the reaction and that the chirality matters. In the absence of a ligand, the product is obtained in a very low yield (<5%), (*S*,*S*)-**L1** proved to be the best ligand with respect to yield, site-selectivity and reaction efficiency. Subsequently, the scope of the arylating agent was tested. Both electron-rich and electron-poor aryl groups give the products in good yield.

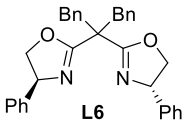
Table 3. Optimization of conditions for the site-selective *O*-arylation of **30**

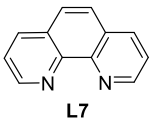


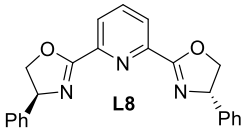
Entry	Deviation from the standard conditions	Yield of **5** [%]	**5/6**
1	none	94	>19:1
2	no $Cu(OTf)_2$	<5	NA
3	no **L1**	<5	NA
4	**L2** instead of **L1**	58	3.9:1
5	**L3** instead of **L1**	5	2.4:1
6	**L4** instead of **L1**	81	>19:1
7	**L5** instead of **L1**	3	>19:1
8	**L6** instead of **L1**	3	NA
9	*ent*-**L1** instead of **L1**	56	2.2:1
10	**L7-L9**	<5	NA
11	**L10** instead of **L1**	55	13:1
12	CuI instead of $Cu(OTf)_2$	82	>19:1
13	K_2CO_3 instead of Et_3N	<5	NA
14	iPr_2NEt instead of Et_3N	92	>19:1

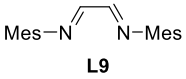


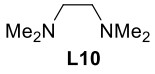






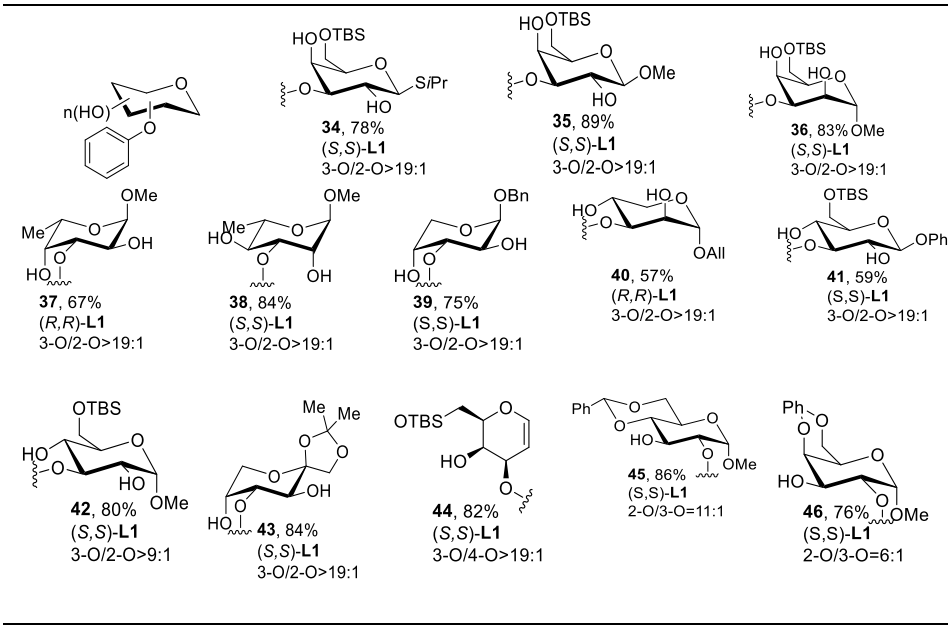


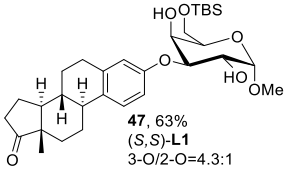


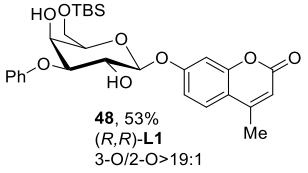


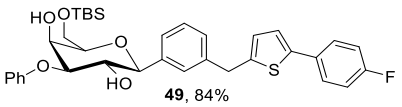
They extended this method on 17 substrates derived from various types of carbohydrates as shown in table 4. Of these, 14 substrates yielded the C3-OH arylated product and only 3 examples **45, 46** and **50** afforded C2-OH arylated product as major product.

Table 4. Scope of the reaction

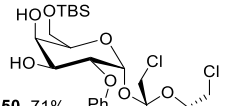






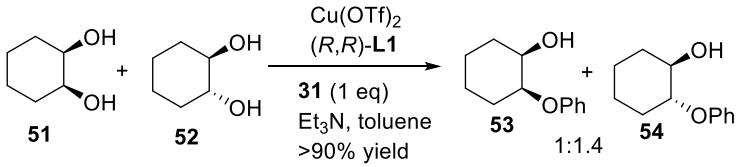


49, 84%
(*S*,*S*)-**L1**
3-O/2-O>19:1



50, 71%
(*S*,*S*)-**L1**
2-O/3-O=9:1

The latter maybe attributed to steric effects in these substrates. The reason why the reaction has so good selectivity was initially tought to be that *cis*-diols are generally considered to chelate metal ions better than *trans*-diols. However, it was soon found that the chelation of copper is not a primary reason for the high selectivity for C3-OH. In a competition experiment of **51** and **52**, the ratio of the products **53** and **54** is 1:1.4. That means (±)-*trans*-1,2-cyclohexanediol **52** was slightly more reactive than *cis*-1,2-cyclohexanediol **51** under the reaction conditions. So it demonstrates that the difference in reactivity of *trans*-diols and *cis*-diols are not the reason for the high selectivity. What was left to conclude was, that selectivity is controlled "by electronic and steric effects". I agree with this as the importance of the ring oxygen in pyranoses on the regioselectivity in palladium catalyzed oxidations has been convincingly demonstrated by Eisink *et al*.. [17]

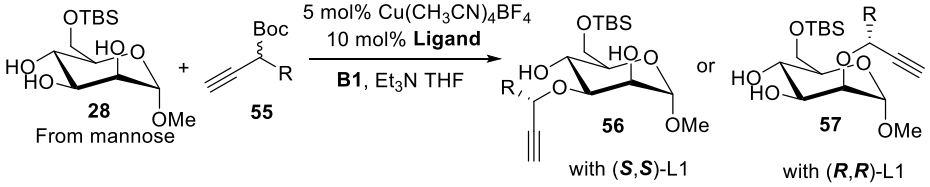


Scheme 7. A competition experiment

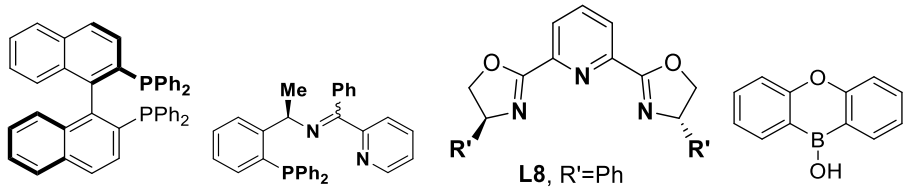
Bols and co-workers[18] compared the p*K*a values of 32 aminosugars, and concluded that the C3-OH has the highest electron density (and therefore the highest pKa) among all secondary hydroxy groups in various carbohydrates. On the basis of this, they attributed the high site-selectivity to the C3-OH of carbohydrates to this high electron density. The ligand makes the substrate react efficiently to enable moderate to high site selectivity.

In the same year, Niu *et al*[19] reported two distinct catalysts that selectively introduce a terminal propargyl group to hydroxyls of diverse monosaccharides and glycosylated compounds with only partial protection. They examined this reaction on mannose derivative **28** (Scheme 8). Supposed that the *cis*-1,2-diol chelated with borinic acid **B1**, the terminal propargyl group can

be introduced to 2-OH or 3-OH via selectively activating one of these groups. Propargyl carbonate was selected as the electrophile. The optimization shows that mannose derivative **28** was treated with **B1** (30 mol%) and ligand **L13** (10 mol%), the reaction gives the best yield, the ratio of **56** and **57** is 13:1, if the ligand **L13** was replaced by ***ent*-L13**, the ratio was changed to 1:20. Then various substrates were studied to define the scope of the reaction, and they applied this reaction on galacto-, xylo-, fuco-, arabino-, fructo-, and ribo-type sugars, all the substrates gave the expected results via the control of the ligand **L13** or ***ent*-L13**.

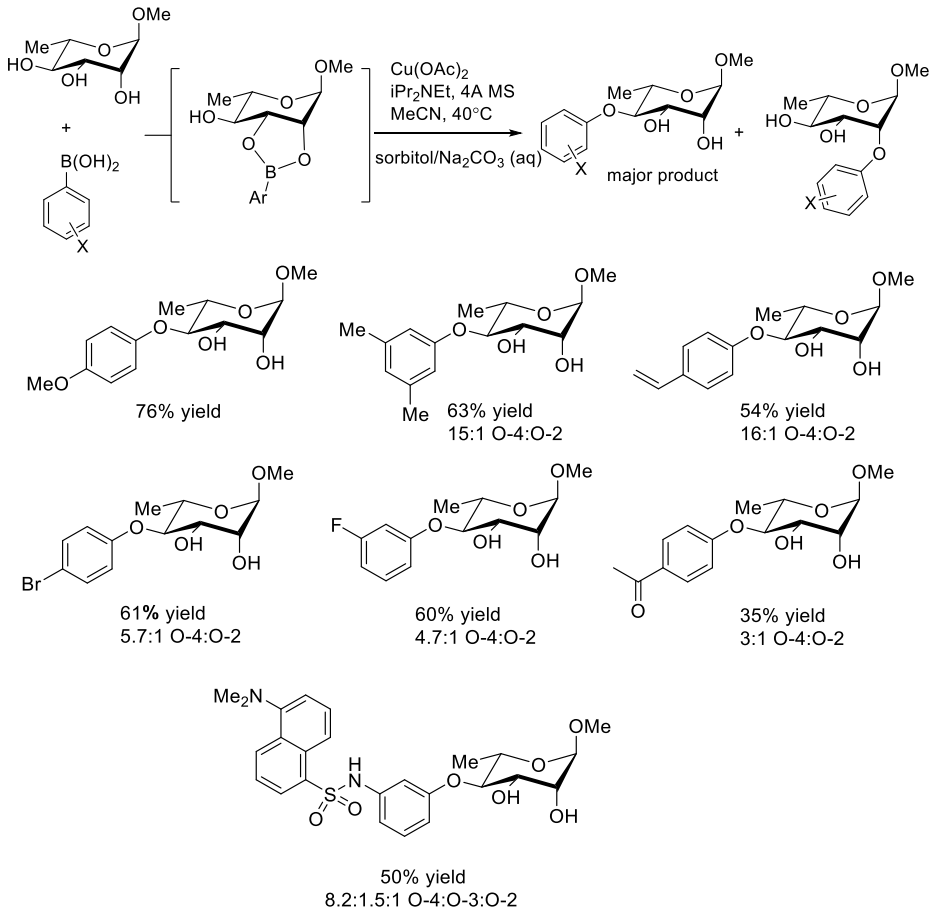


Entry	**Ligand**	**R**	Loading of **B1**	Temp (℃)	Yield (major isomer)	Ratio (**18a**:**18b**)
1	**L11**	Ph	5%	-20	<5%	N.D
2	**L12**	Ph	5%	-20	<5%	N.D
3	**L8**	Ph	5%	-20	26%	9:1
4	**L13**	Ph	5%	-20	31%	13:1
5	**L13**	Ph	30%	-20	53%	13:1
6	**L13**	Ph	30%	25	48%	6:1
7	**L13**	Ph	30%	-20	82%	13:1
8	***ent*-L13**	Ph	30%	-20	63%	1:11
9	**L13**	Ph	**no B1**	-20	<5%	N.D
10	**no ligand**	Ph	30%	-20	<5%	N.D
11	**(±)-L13**	Ph	30%	-20	40%	2.8:1
12	**L13**	*o*-Tol	30%	-20	76%	20:1
13	***ent*-L13**	*o*-Tol	30%	-20	74%	1:20



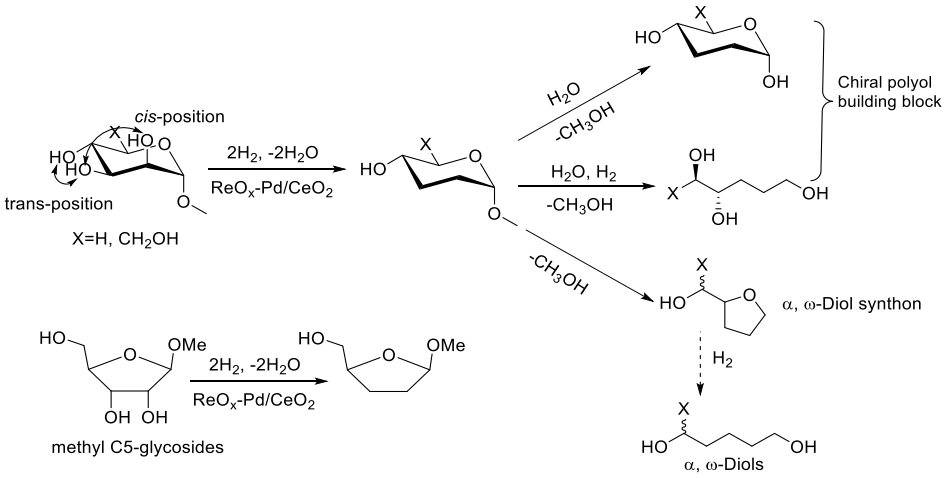
Scheme 8. The propargylation of a mannose derivative

Taylor *et al*[20] also reported selective *O*-arylation of carbohydrates deriavatives by a copper catalysts. Methyl α-L-rhamnopyranoside was selected as a substrate for investigation. When it was treated with phenylboronic acid, $Cu(OAc)_2$ (2 eq), diisopropylethylamine, and 4 Å molecular sieves, it gave 4-*O*-arylated product with high selectivity. Various arylboronic esters were tried in the reaction, all the examples majorly gave 4-*O*-arylated product. The results show that electron-deficient arylboronic acids increased the ratio of 2-*O*-arylated side product (Scheme 9).



Scheme 9. Copper-mediated site-Selective installation of substituted aryl ethers

1.3.3 Site-selective deoxygenation of sugars with H_2 over heterogeneous catalysts



Scheme 10. Transformation methods of methyl glycosides

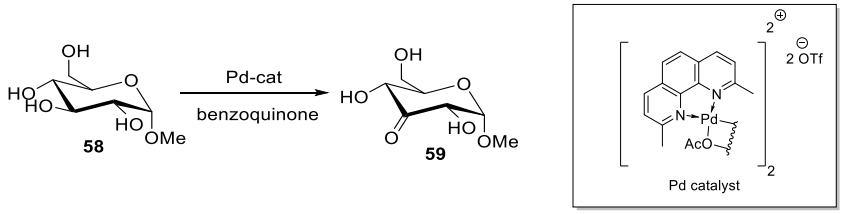
The removal of hydroxyl groups (deoxygenation) in sugars also has gained attention, because deoxy sugars are structural elements of natural products and deoxygenated sugars can be also scaffolds for medicines[21, 22] and for green chemistry building blocks. A famous example is 2-deoxyribose, serving as a precursor of the nucleic acid DNA. Another example is L-fucose, the constituent of *N*-linked glycans on the mammalian, insect and plant cell surface. As for other modifications on the carbohydrate core, the conventional synthesis of deoxy sugars relies on complicated protection and deprotection schemes.[21] Although this strategy provides access to the desired target molecules, the major drawbacks are that it is time consuming, uneconomic and not suitable for disaccharides/oligosaccharides. Protecting group-free preparation of deoxy sugars by catalytic and selective transformations of the OH groups forms an attractive alternative.[23] In this process, it is essential that the catalyst recognizes one or more hydroxyl groups in the sugar. Deoxydehydration (DODH) is a versatile way to remove vicinal OH groups in polyols and affords the corresponding olefins.[24-30] Keiichi *et al.*[23,31] reported deoxydehydration-hydrogenation (DODH-HG) of glycerol, erythritol, xylitol, sorbitol and 1,4-anhydroerythritol. It is an efficient strategy to remove vicinal OH groups in diols in a one-pot reaction to generate the dideoxy product. In their method (as depicted in scheme 10), the catalyst ReO_x-Pd/CeO_2 used H_2 as the reducing agent, and C-C bond cleavage was not observed. The developed ReO_x-Pd/CeO_2 catalyst recognizes *cis*-vicinal diols selectively in methyl glycosides, and removes *cis*-

vicinal diols to give dideoxy glycosides using H_2.[32] The resulting dideoxy glycosides are readily transformed into useful chiral building blocks and α,ω-diol synthons (Scheme 10). The research shows that methyl hexopyranosides with *cis*-vicinal OH groups react to form the corresponding dideoxy products, while methyl hexopyranosides containing solely *trans*-OH do not. On methyl C5-glycosides (Scheme 10) the same result was obtained. Only C5-glycosides with *cis*-vicinal OH groups give the corresponding dideoxy product and compared with *cis*-C6, methyl β-D-ribofuranoside, *cis*-C5 has a higher reactivity. In their paper, they mentioned that the catalyst could be used four times without loss of activity and selectivity.

1.3.4. Catalytic regioselective oxidation of carbohydrates

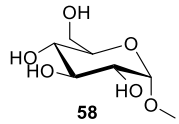
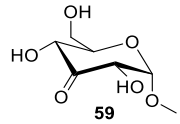
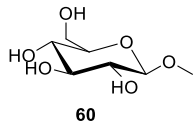
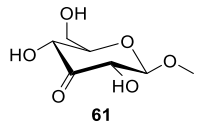
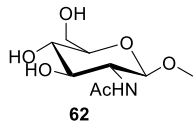
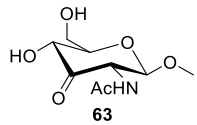
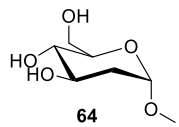
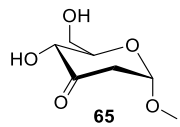
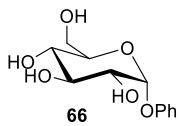
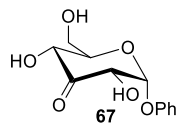
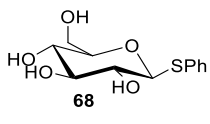
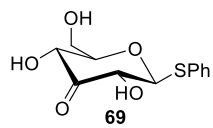
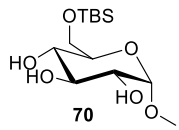
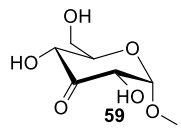
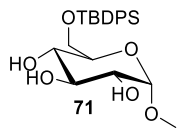
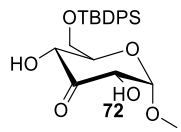
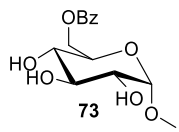
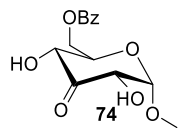
A protecting group strategy is useful in the oxidation of carbohydrates. All hydroxyl groups are protected to leave one hydroxyl group to be oxidized.. Selective oxidation of carbohydrates is challenge in carbohydrate chemistry. The selective of oxidation of the primary hydroxyl group in glycosides by chemical[33] or enzymatic[34] means has been described. The selective oxidation of one of the secondary hydroxyl groups is difficult because of the small differences in the reactivity of the secondary hydroxyl groups.

In 2013, our group reported on the selective catalytic oxidation of glycosides.[35] We found that treating methyl α-D-glucopyranoside **58** with the catalyst [(neocuproine)Pd(OAc)]$_2$(OTf)$_2$ and stoichiometric benzoquinone in aqueous acetonitrile afforded 3-keto glycoside **59** in nearly quantitative yield. (Scheme 11).



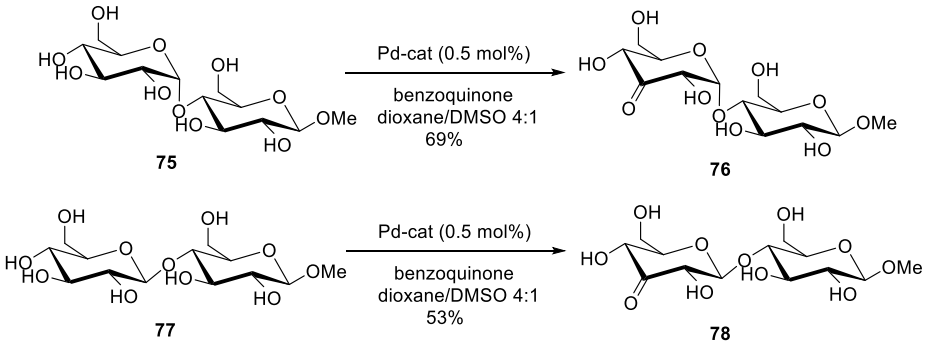
Scheme 11. Selective oxidation of methyl α-D-glucosides and the structure of the Pd-catalyst

Table 5. The selective catalytic oxidation of monosaccharides.

Entry	Substrate	Product	Method	Yield [%]
1	 **58**	 **59**	A	96%
2	 **60**	 **61**	A	85%
3	 **62**	 **63**	A	89%
4	 **64**	 **65**	B	60%
5[C]	 **66**	 **67**	B	73%
6	 **68**	 **69**	C	47%
7[d]	 **70**	 **59**	A	96%
8	 **71**	 **72**	D	66%
9	 **73**	 **74**	D	45%

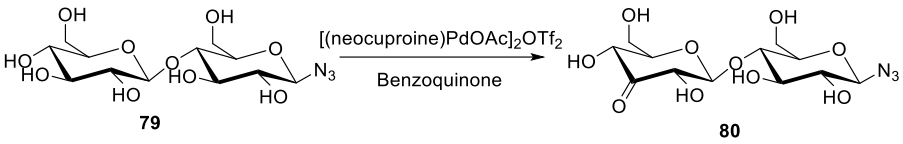
[a] Method A: pyranoside (4 mmol), Pd-cat (2.5 mol%), DCBQ (3 equiv), MeCN/H_2O 10:1, 0.3M. Method B: pyranoside (0.8 mmol), Pd-catalyst (2.5 mol%), DCBQ (3 equiv), dioxane/DMSO 4:1, 0.3M. Method C: pyranoside (0.8 mmol), Pd-catalyst (6.5 mol%) added in portions, DCBQ (3 equiv), dioxane/DMSO 4:1, 0.3M Method D: pyranoside (0.8 mmol), 1 (2.5 mol%), DCBQ (3 equiv), DMSO, 0.3M. [b] Yields of isolated products. [c] 10 (0.4 mmol). [d] The TBS group was

cleaved under the reaction conditions. TBS=tert-butyldimethylsilyl, TBDPS=tert-butyldiphenylsilyl



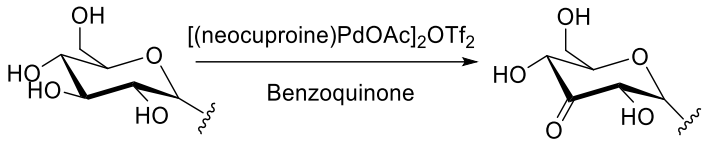
Scheme 12. Selective oxidation of methyl β-D-maltoside and methyl β-D-cellobioside

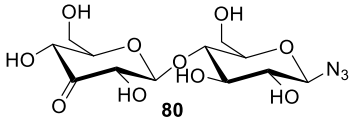
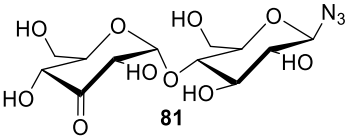
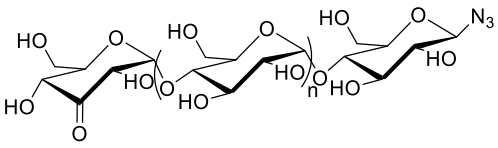
In a follow-up paper, we showed that the method could be extended to longer 1,4 glucans.[36] A series of glycosyl azides that was prepared with 2-chloro-1,3-dimethylimidazolinium chloride (DMC see chapter 1.2.1) according to Shoda's method[3,4,10,37,38] was subjected to catalytic selective oxidation (table 6 and scheme 13). Initial oxidation experiments failed because the starting material contained trace amounts of NaN_3, NaCl, NaBr and KI, which inhibit the reaction. To reduce the amount of chloride, DMC chloride was replaced by DMC PF_6. Furthermore, the azido glycosides were purified by charcoal column to remove the salts carefully. All the azido oligosaccharides reached the full con version in the subsequent oxidation. Interestingly, NMR studies showed that all the substrates are selectively oxidized at C3-OH of the terminal glucose residue.[36] Besides glycosides, we showed that reducing saccharides could be used as substrate as well. α-D-glucose and *N*-acetyl-α-D-glucosamine could be transformed selectively into the corresponding keto sugar without the oxidation of the anomeric position.[39] β-Glucose, which possesses a vicinal bis-equatorial diol at the anomeric center, was oxidized at the C1 and the C3 position. The resulting ketolactone intermediate **87** tautomerizes rapidly to ene-diol **88** and oxidized further to diketolactone **89**. This intermediate subsequently underwent intramolecular lactol formation and finally via α-ketol rearrangement gave **91** (Scheme 14). To oxidize α-glucose selectively, it is thus essential to avoid mutarotation and the reaction therefore has to be performed in DMSO.



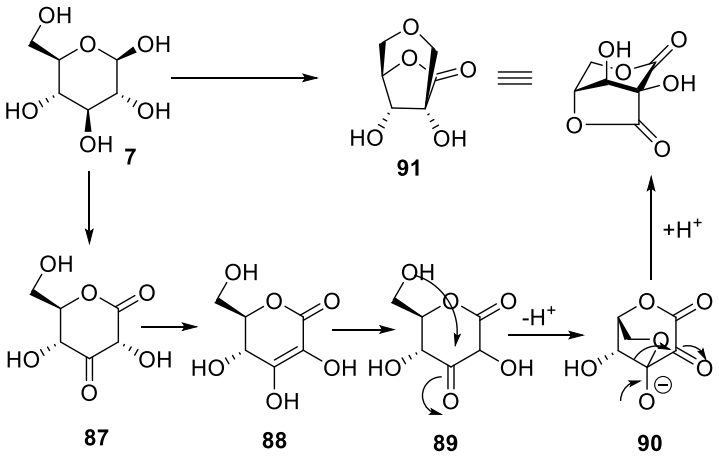
Scheme 13. Oxidation of β-D-cellobiosyl azide **79**

Table 6. Regioselective oxidation of oligomaltosyl azides



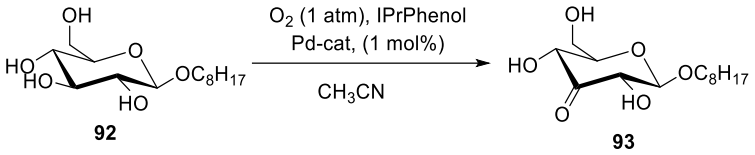
Entry	Product	Yield (%)
1	 **80**	61
2	 **81**	59
3-7		**82a** n=1: 60 **83a** n=2: 38 **84a** n=3: 30 **85a** n=4: 30 **86a** n=5: 47

Reaction conditions: 7.5 mol% of $[(neocuproine)PdOAc]_2OTf_2$, 3eq. of benzoquinone, 0.3 M in DMSO/dioxane 1:4, r.t. 7h. [a] 15 mol% of $[(neocuproine)PdOAc]_2OTf_2$, 3eq. of benzoquinone, 0.3 M in DMSO



Scheme 14. Oxidation of β-D-Glucose Leads to Rearranged Bislactone

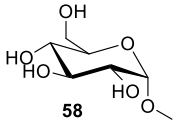
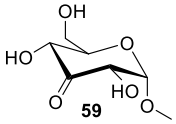
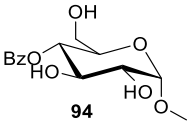
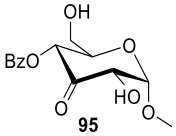
At the same time, Waymouth and coworkers[40] investigated the feasibility of oxidizing monosaccharides with the $[(neocuproine)Pd(OAc)]_2(OTf)_2$ catalyst (scheme 15) using oxygen as a terminal oxidant. Replacing benzoquinone by oxygen simplifies the purification of the keto products, but a higher Pd loading of 10 mol % was required since aerobic oxidation results in the oxidative degradation of the ligand as well.[41-44] The addition of a sacrificial reductant, such as 2,5-diisopropylphenol, to the reaction mixture suppressed this undesired degradation somewhat and improved the catalyst lifetimes. In the presence of the additive, the selective oxidation could be carried out in acetonitrile, acetonitrile/water or trifluoroethanol with oxygen and lower Pd loadings. Waymouth and coworkers[40] applied their optimized conditions on 6-deoxy-glycopyranosides, xylopyranosides, 1,6-anhydropyranoses and arabinopyranosides. Interestingly, hexopyranosides bearing an axial hydroxy substituent, as well as xylopyranosides could be oxidized selectively at C3 under these conditions. For some glycosides, especially those that have an axial hydroxyl at C4, minor amounts of 4-ketoses were formed. The selectivity could be increased by performing the reaction in trifluoroethanol, but axial hydroxyl groups at the C2 or C4 tended to epimerize to the equatorial position under these conditions.

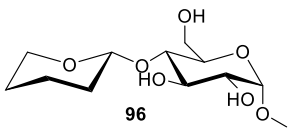
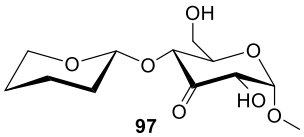
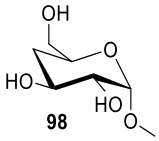
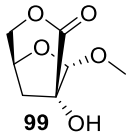
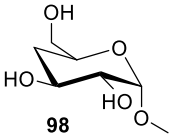
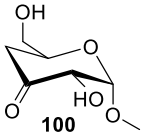


Scheme 15. Catalytic oxidation by oxygen.

The outcome of Waymouth's and our studies provided important insight in the factors that determine the regioselectivity of the reaction. The configuration and the nature of the substituent at the anomeric center C1 is not relevant for the selectivity. Furthermore, neither the OH group at C2, nor the primary C6 OH does influence the selectivity of the oxidation. Removal of either of these groups still results in selective oxidation of the C3 OH. Competition experiments between methyl glucopyranoside **58** and methyl 2-deoxy-α-D-glucopyranoside **64** with limiting benzoquinone confirmed that the presence of a *trans* equatorial vicinal diol on C3-C4 is sufficient to obtain selective oxidation at the C3. Also the CH_2OH at C5 is not essential. Furthermore, the work of Waymouth and co-workers[40] showed that oxidation of monosaccharides containing *cis* diols is feasible. However, methyl β-D-galactopyranoside and methyl α-D-mannopyranoside gave a complex mixture, even when optimized conditions were used, indicating that additional factors determine the outcome of the reaction for these substrates. Moreover, it is from this panel of substrates not apparent (1) why oxidation occurs exclusively at the terminal glucose residue of 1,4-linked glucans and (2) why the C3 OH oxidizes selectively. Our group recently addressed these question by carefully studying the oxidation of monosaccharide analogs with qNMR.[45]

Table 4. Selective Oxidation of C4-modified Glucopyranosides[a]

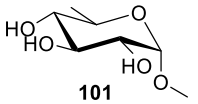
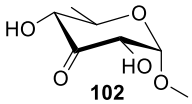
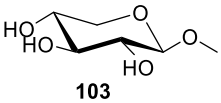
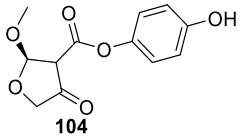
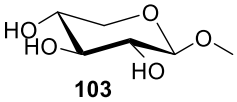
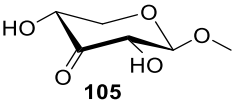
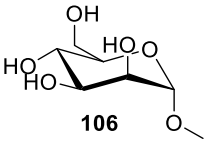
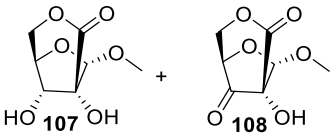
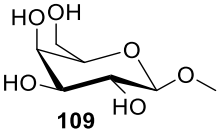
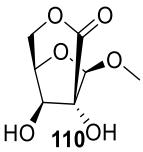
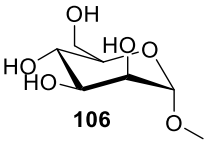
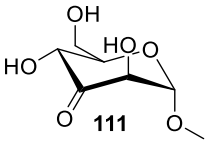
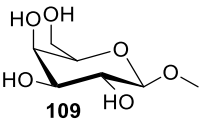
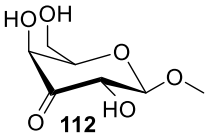
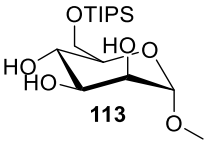
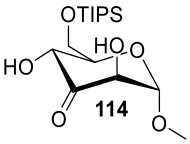
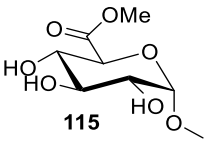
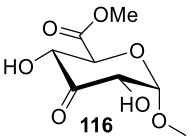
#	SM	Product	Selectivity
1	 **58**	 **59**	87%
2	 **94**	 **95**	78%[b]

3	 **96**	 **97**	70%
4	 **98**	 **99**	57%
5	 **98**	 **100**	94%[c,d]

[a]Reaction conditions: 2.5 mol % of $[(neocuproine)PdOAc]_2OTf_2$, 3 equiv of benzoquinone, 0.3 M in DMSO-d_6. Selectivity determined by qNMR using the residual DMSO-d_6 as an internal standard. Unless otherwise stated, no other products could be assigned by ^1H NMR, with an estimated detection limit of 3%. [b]Incomplete conversion, 72% conversion of starting material. Selectivity calculated according to this conversion. [c]Performed with 1 equiv of benzoquinone. [d]Incomplete conversion, 68% conversion of starting material. Selectivity calculated according to this conversion.

Based on the hypothesis that the most important difference between the internal glucose residues and the terminal residue is that the C4 OH is linked to the anomeric center of the adjacent monosaccharide, we prepared glucopyranoside analogs that mimic the internal residues.[45] We investigated the influence of the steric hindrance that the substituents at C4 imposed on the C3 OH by synthesizing C4-benzoyl (**94**) and C4-THP (**96**). We determined the effect of the substituent on chelation with methyl 4-deoxyglucopyranoside **98**. qNMR revealed that all mimics gave the corresponding product C3 keto products (**95**, **97** and **100**). These results suggested that oxidation of internal glucose residues of 1,4-oligoglucoses could occur and that most likely a difference in reaction rate was at the basis of the selectivity. Competition experiments with methyl α-D-glucopyranoside **58** and the substrates depicted in table 4 with a limiting amount of benzoquinone relative to the total amount of glycoside supported this reasoning. Derivatives with a bulky group at the C4-OH, such as the THP, reacted significantly slower than non-substituted derivative **58** in the competition experiment. On the contrary, derivatives that lack a hydroxyl group at the C4 oxidize with a similar rate as methyl α-D-glucopyranoside **58**. These results clearly indicate that the selectivity for terminal glucose residue in 1,4-linked glucans is controlled by sterics.

Table 5. Regioselective Oxidation of (Modified) Glucopyranosides, Mannopyranosides, and Galactopyranosides

Entry	SM	Product	Selectivity
1	 **101**	 **102**	69%
2	 **103**	 **104**	38%
3	 **103**	 **105**	64%[b]
4	 **106**	 **107** + **108**	26%+19%
5	 **109**	 **110**	27%
6	 **106**	 **111**	30%[b]
7	 **109**	 **112**	21%
8	 **113**	 **114**	81%[b,c]
9	 **115**	 **116**	82%[d]

[a]Reaction conditions: 2.5 mol % of [(neocuproine)PdOAc]$_2$OTf$_2$, 3 equiv of benzoquinone, 0.3 M in DMSO-d_6. Selectivity determined via qNMR using the residual DMSO-d_6 as an internal

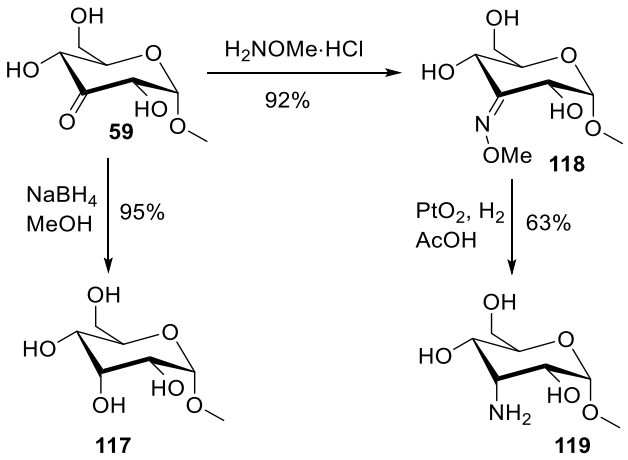
standard. Unless otherwise stated, no other products could be assigned by ^{1}H NMR, with an estimated detection limit of 3%. [b]Performed with 1 equiv of benzoquinone. [c]Incomplete conversion, 58% conversion of starting material. Selectivity calculated according to this conversion. [d]Isolated yield.

The qNMR studies also helped to establish why galactosides and mannosides yielded a complex mixture in the Pd-catalyzed oxidation reaction. The observations that β-D-glucose underwent ring contraction after the initial oxidation and that xyloside **103** could be oxidized selectively with oxygen or a stoichiometric amount benzoquinone led to the hypothesis that galactosides and mannosides suffered from over-oxidation, rather than a lack of selectivity. Indeed, oxidation of galactosides and mannosides with a minimal amount of benzoquinone gave the C3 oxidized products **111** and **112**, albeit that the selectivity is lower. NMR showed that the C6-OH of these glycosides rapidly attacked the newly formed carbonyl, which caused over-oxidation and ultimately led to rearrangement products. The fact that locking mannose and galactose in their 1,6-anhydro form circumvents over-oxidation supports this reasoning. Moreover, protection of the C6-OH in mannose with a TIPS group also prevents intramolecular nucleophilic attack and indeed also suppressed side reactions. Competition experiments between glucopyranoside **58** and galactopyranoside **109** or mannopyranoside **106** also gave an indication why these side reactions take over for these substrates. Both substrates reacted considerably slower, indicating that the axial hydroxyl groups at C2 or C4 position deactivate the substrate. Together with the reduced stability of the chair conformation in these sugars, this causes the intramolecular hemiacetal formation to take over.

1.4. Modification at C3 via catalytic oxidation

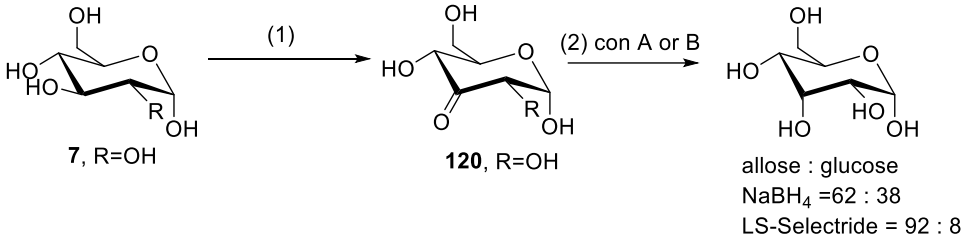
Site selective oxidation of a carbohydrate yields ketone bearing mono-, di- and oligosaccharides. A plethora of reactions has been developed that allow the further modification of the keto group in the presence of the hydroxyl groups and this chemistry will enable the further modification of the keto saccharides. For example, stereoselective reduction of the ketone should enable the straightforward interconversion of common monosaccharides into rare sugars. Indeed, methyl α-D-allose **117** and allose, could be synthesized via oxidation and reduction of glucopyranoside **59** and α-glucose, respectively.[35,39] Reduction of

methyl 3-ketone glucose **59** with $NaBH_4$ yielded methyl allose **117** in 95% (Scheme 16).



Scheme 16. Synthesis of methyl α-D-allose and methyl 3-epi-kanosamine

For the synthesis of allose from glucose (Scheme 17), the crude 3-ketoglucose in DMSO was treated with a solution of $NaBH_4$ in H_2O at 0 °C, which afforded a 3:2 mixture of allose and glucose. By switching the reducing agent to LS-selectride, allose was obtained with a high selectivity.



Scheme 17. (1)Reaction conditions: $[(neocuproine)PdOAc]_2OTf_2$ (0.5 mol%), benzoquinone (1.25 equiv), 1.5 M in DMSO, rt, 1h. (2) Reaction conditions: (A) $NaBH_4$ (0.75 equiv), DMSO/H_2O (1:1), 0°C; (B) LS-selectride (3 equiv), DMSO/THF (2:1), 0°C

The ketone could also be functionalized by reductive amination.[35] Methyl 3-amino-3-deoxy-α-D-allose **119** (Scheme 16) was prepared using methyl 3-ketone glucose **59** as starting material. Compound **59** is transformed to its corresponding *O*-methyl oxime **118**, followed by the reduction of **118** with H_2/Adam's catalyst

to generate methyl 3-epi-kanosamine **119**. The synthesis is two steps in 58% overall yield with only one isomer.[35]

1.5 Aim and Outline of this thesis

Aim

The synthesis of rare sugars and modified sugars is often accompanied by a considerable number of steps and the use of protecting groups. Recently, catalytic oxidation of glycosides to generate the corresponding 3-ketoses has opened the door to a variety of modifications. This is not only restricted to the synthesis of rare sugars, but also has the potential to allow further modification of the keto group provided the reaction conditions are compatible with the presence of free hydroxyl groups. This holds, among others, for multicomponent reactions such as the Passerini reaction. Next to this, we applied a recently developed reductive chlorination reaction to 3-ketoses. After two initial studies on the application of multicomponent reactions on carbohydrates, the major focus of this thesis is on the modification of the ketose after the catalytic oxidation, as it provides new access to modified glycosides without protection.

Outline

Chapter 2 describes the use of tert-butyl carbazate as the amine part in the Ugi tetrazole reaction.

Chapter 3 describes a novel approach to prepare sugar isocyanides and their application to isocyanide-based multicomponent reactions.

Chapter 4 describes a method to prepare the rare sugars allosamine, and lividosamine, diamino sugars and related compounds based on the site-selective catalytic oxidation of isopropyl *N*-acetyl-α-D-glucosamine.

Chapter 5 describes the synthesis of the antibiotic compound streptozotocin and its C3 derivatives with the aim to reduce its toxicity to β-cells.

Chapter 6 describes the conversion of 3-ketoses prepared from mono- and disaccharides to the corresponding trityl hydrazones, followed by their reductive chlorination.

Chapter 7 is an outlook and future perspective on the selective oxidation of glycosides. Several possible modifications of 3-keto sugars are given, a new method to prepare complicated sugars will be introduced on the basis of the work in chapter 6.

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